Respiratory Medicine (2012) 106, 34–46

Available online at www.sciencedirect.com

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The efficacy and tolerability of MK-0633, a 5-lipoxygenase inhibitor, in chronic asthma

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Received 6 June 2011; accepted 20 August 2011
Available online 25 September 2011

KEYWORDS
Asthma;
Leukotrienes;
5-Lipoxygenase

Summary
Leukotriene B4 (LTB_4) is a potent inflammatory mediator in asthma, and is increased in more severe asthma. Targeting LTB_4, in addition to cysteinyl leukotrienes, could be beneficial in asthma.

This was a randomized, double-blind trial of once-daily MK-0633, a potent 5-lypoxygenase inhibitor, 10 mg, 50 mg, and 100 mg, and placebo in patients 18–70 years with a history of chronic asthma, and FEV_1 ≥45 and ≤85% predicted. There was a 6-week main period and optional 18-week and 34-week periods (52 weeks total), the latter two comparing only MK-0633 100 mg and placebo. The primary endpoint was the change from baseline in FEV_1 over the last 4 weeks of the 6-week primary treatment period. Secondary endpoints included symptom scores, β-agonist use, peak expiratory flow (PEF), asthma quality of life questionnaire (AQLQ), asthma control questionnaire (ACQ), asthma attacks, exacerbations, days with asthma control, post-β-agonist FEV_1, and blood eosinophils.

MK-0633 100 mg was significantly more effective than placebo for the change from baseline in FEV_1 (0.20 L vs. 0.13 L; $p = 0.004$). The other MK-0633 doses were not significantly more effective than placebo. MK-0633 (at various doses) was also more effective than placebo for β-agonist use, AQLQ, AM and PM PEFR, ACQ, and post-β-agonist FEV_1 ($p < 0.05$ for all). MK-0633 was associated with a dose-dependent increase in elevated aspartate aminotransferase and alanine aminotransferase.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2011.08.019

Because of the relative benefit-risk ratio, the optional study periods were terminated after unblinding for the main study period. Overall, the benefit-risk ratio did not support the clinical utility of MK-0633 in asthma.

Introduction

Despite advances in asthma management and education initiatives, the proportion of patients achieving adequate asthma control continues to be suboptimal.[1,2] In one study specifically designed to evaluate guideline-based asthma treatments in patients with uncontrolled asthma, after a year of treatment, fewer than 75% of patients had well-controlled asthma, and only approximately one-third achieved total asthma control, even though most patients were receiving the maximum doses of either inhaled fluticasone or inhaled fluticasone plus salmeterol.[3] In addition, a cross sectional study in Canada evaluating asthma control (as defined by healthcare resource utilization, β-agonist use, nighttime awakenings, and missed school or work) revealed that asthma control did not improve between 1997 and 2002.[4] Thus, there continues to be a need for new therapeutic options in asthma.

The central role of leukotrienes in asthma is well-established.[5] 5-lipoxygenase (5-LO) and 5-LO activating protein (FLAP) catalyze the conversion of arachidonic acid to leukotriene A_4 (LTA_4), which in one pathway is converted to LTB_4, and in another pathway to LTC_4, which is further converted to LTD_4 and LTE_4.[5,6] LTC_4, LTD_4, and LTE_4, collectively known as the cysteinyl leukotrienes (CysLTs), are produced primarily by mast cells, macrophages, and eosinophils, and play a key role in bronchoconstriction, airway edema and mucus secretion. LTB_4, on the other hand, is synthesized primarily by neutrophils and is a potent chemoattractant and inflammatory mediator thought to play a significant role in early immune system activation and T-cell recruitment,[7] as well as neutrophil and macrophage recruitment and activation.[8,9]

LTB_4 may be a particularly important mediator in more severe asthma. Studies have demonstrated that, compared to patients with mild to moderate asthma, patients with severe asthma had significantly increased concentrations of neutrophils in bronchoalveolar lavage,[10] and induced sputum.[11,12] Clinically, the potential role of neutrophils and LTB_4 in severe asthma is supported by a post-hoc analysis of two studies of the 5-LO inhibitor zileuton, which showed substantially greater effects versus placebo on forced expiratory volume in 1 s (FEV_1) and on the percentage of patients requiring oral corticosteroid rescue in patients with severe asthma (baseline FEV_1 $\leq$50% predicted) compared with the full patient cohort.[13,14]

These results also highlight the potential utility of inhibiting leukotriene synthesis (i.e., 5-LO or FLAP), and thus inhibiting both LTB_4 and CysLTs. Given the distinct effects of CysLTs and LTB_4 in asthma, an agent that inhibits both products would theoretically confer greater protection in chronic asthma, with the potential for enhanced efficacy among severe asthmatics. Zileuton is the only leukotriene synthesis inhibitor approved to date. Its use has been limited hepatic enzyme monitoring and q.i.d. dosing,[14] although it is now available as a controlled-release, b.i.d. formulation.

The purpose of this Phase II trial was to evaluate the efficacy and tolerability of MK-0633, a potent, once-daily 5-LO inhibitor, in adults with chronic asthma.

Methods

Full methodological details are available in the Online Supplementary material.

Patients

Men and women age 18—70 years with a history of chronic asthma for at least 1 year were eligible. Patients had FEV_1 $\geq$45% and $\leq$85% of the predicted value, and reversibility of $\geq$12% within 20—30 min following β-agonist administration. To determine the efficacy of MK-0633 across the spectrum of asthma severity, patients were stratified as being treated with either (1) a stable dose of inhaled corticosteroid (ICS) or an ICS and long-acting β-agonist (LABA) combination for at least 4 weeks preceding screening (approximately 2/3 of subjects, who continued with this concomitant therapy at a stable dose during the trial), or (2) only as-needed short-acting β-agonists (approximately 1/3 of subjects). This stratification plan was chosen to maximize the percentage of patients with more severe asthma that was not adequately controlled, which was the primary population of interest. Excluded asthma medications included inhaled long-or short-acting anticholinergic agents within 2 weeks; ICS within 4 weeks of the screening visit, or oral or inhaled LABAs within 1 week (if patient was not included in the 2/3 of patients in the ICS or ICS/LABA group); oral, intravenous, intramuscular, or rectal corticosteroids within 4 weeks; xanthine derivatives or combinations within 2 weeks, antileukotrienes within 2 weeks, or omalizumab within 4 weeks.

Inhaled albuterol/salbutamol was permitted on an as-needed basis for relief of asthma symptoms. An action plan for worsening asthma was provided.

Study design (Fig. 1)

This study (Merck Protocol 007, ClinicalTrials.gov identifier NCT00404313) was a 6-week, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study of MK-0633, conducted at 154 multinational sites from March 2008 to June 2009. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All patients provided written informed consent prior to participation.

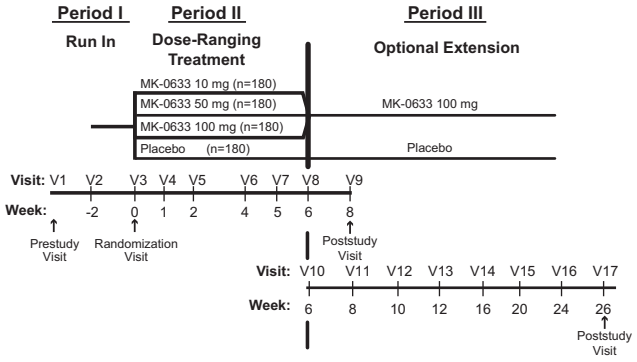

Figure 1 Study design.

During a 2-week, single-blind, placebo run-in period (Period I), patients were required to meet minimum asthma symptom requirements and have at least 80% compliance with study medication as determined by pill count. Eligible patients were randomized to once-nightly MK-0633 10 mg, 50 mg, 100 mg, or matching placebo for 6 weeks (Period II). Two optional double-blind extensions comparing MK-0633 100 mg and placebo followed: an 18-week (24 weeks total) extension (Period III), and a 34-week (52 weeks total) extension (Period IV). Patients on active treatment (any dose) in Period II received MK-0633 (100 mg) in Periods III and IV, and patients receiving placebo in Period II continued to receive placebo in Periods III and IV.

Allocation was determined according to a computer-generated schedule. Numbered vials were used to implement allocation. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel remained blinded to treatment allocation throughout the study. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

Efficacy and tolerability assessments

Spirometry was performed in accordance with ATS criteria standards of acceptability and quality control.[15] A standard spirometer (NDD) was provided. Measurements were performed at baseline/randomization and at weeks 1, 2, 4, 5, and 6 between 6 AM and 10 AM after withholding short-acting β-agonists for at least 6 h, ICS for at least 12 h, and ICS/LABA for at least 14 h. The largest FEV_1 and FVC from acceptable and reproducible maneuvers were used for the analyses. A daily patient diary was used to capture daytime and nighttime symptoms, β-agonist use, peak expiratory flow rate (PEFR), and asthma resource utilization. Patients also completed the Asthma Quality of life Questionnaire (AQLQ)[16] and Asthma Control Questionnaire (ACQ).[17]

The primary efficacy endpoint was the change from baseline in FEV_1 (pre-β-agonist) over the last 4 weeks of the 6-week treatment period. Secondary endpoints were the change from baseline in daytime and nighttime symptom scores over the last 4 weeks of treatment. Other endpoints included as-needed β-agonist use, AM and PM PEFR, change in AQLQ and ACQ scores, the percentage of patients with asthma attacks, asthma exacerbations, percentage of days with asthma control; post-β-agonist FEV_1; and average total peripheral blood eosinophils counts. Exploratory endpoints included the pharmacokinetic measurements of MK-0633, change from baseline in urine LTE_4 excretion, and plasma biomarkers [e.g., immunoglobulin E (IgE) and eosinophilic cationic protein (ECP)].

Tolerability was assessed by physical and laboratory examinations, vital signs, and incidence of adverse experiences (AEs). Because of a suggestion of renal tubular damage in mice in acute toxicity studies, an internal data safety monitoring committee reviewed results of an interim blinded safety analysis of urine N-acetyl-β-glucosaminidase (NAG), a sensitive marker of acute tubular injury,[18] as well as other markers of renal function, after 50% of patients completed the main study. Any patients found to have NAG elevations $>2\times$ but $<3\times$ from baseline at this blinded interim analysis had their urinary monitoring increased to every 1—2 weeks; patients with NAG $>3\times$ baseline value on 2 consecutive measurements were discontinued. Patients with ALT or AST $\geq 3\times$ ULN on 2 consecutive occasions were also discontinued.

Pharmacokinetic (PK) measurements

Plasma samples were collected for MK-0633 assay at prestudy and at week 6, pre-dose. Urinary LTE_4 samples were collected at baseline and at Week 6.

Statistical methods

The primary hypothesis was that MK-0633, compared with placebo, would result in significant improvement in FEV_1 over the last 4 weeks (weeks 2, 4, 5, and 6) of the 6-week active treatment period. The primary efficacy analysis was based on the Full Analysis Set population, which included all randomized patients who received at least one dose of study treatment and had a baseline and at least one on-treatment FEV_1 measurement. Patients were included in the treatment group to which they were randomized. The primary endpoint was analyzed using weekly changes from baseline in a longitudinal data analysis model with the Tukey linear trend test for assessing dose—response, and included factors for treatment, week, concomitant corticosteroid stratum (none, either ICS or ICS/LABA), and baseline value as covariates. The analyses were based on observed data; missing

values were not imputed. Pre-specified subgroup analyses included gender, age ($\leq$, $>$median), age and gender combined, race (white, black, Hispanic, Asian, other), region (US/Canada, Central/South America, Europe, Japan, other), baseline FEV_1 % predicted ($\leq$, $>$median), severe persistent asthma as defined by the National Asthma Education and Prevention Program (NAEPP) guidelines[19] (yes/no); and severe persistent asthma as defined by the Global Initiative for Asthma (GINA) guidelines[20] (yes/no). A per-protocol analysis would be performed only if more than 5% of patients in the FAS population were protocol violators.

Tolerability analyses were based on the All Patients as Treated population, which included all randomized patients who received at least one dose of study medication. Patients were included in the treatment group corresponding to the study medication actually received, irrespective of the group to which they were randomized. AEs of interest included discontinuations due to worsening of asthma, the percentage of patients meeting NAG criterion for discontinuation, and the percentage of patients with percent change in urinary NAG and microalbumin of $<$100%; 100% to $<$200%; and $\geq$200%. We also collected rates of clinical AEs, drug-related AEs, serious AEs, and discontinuations due to AEs.

The MK-0633 doses were compared with placebo using a stepwise linear trend test, which was dependent on a significant effect at the 100 mg dose before comparing the effect at the 50 mg dose and, if significant, at the 10 mg dose.

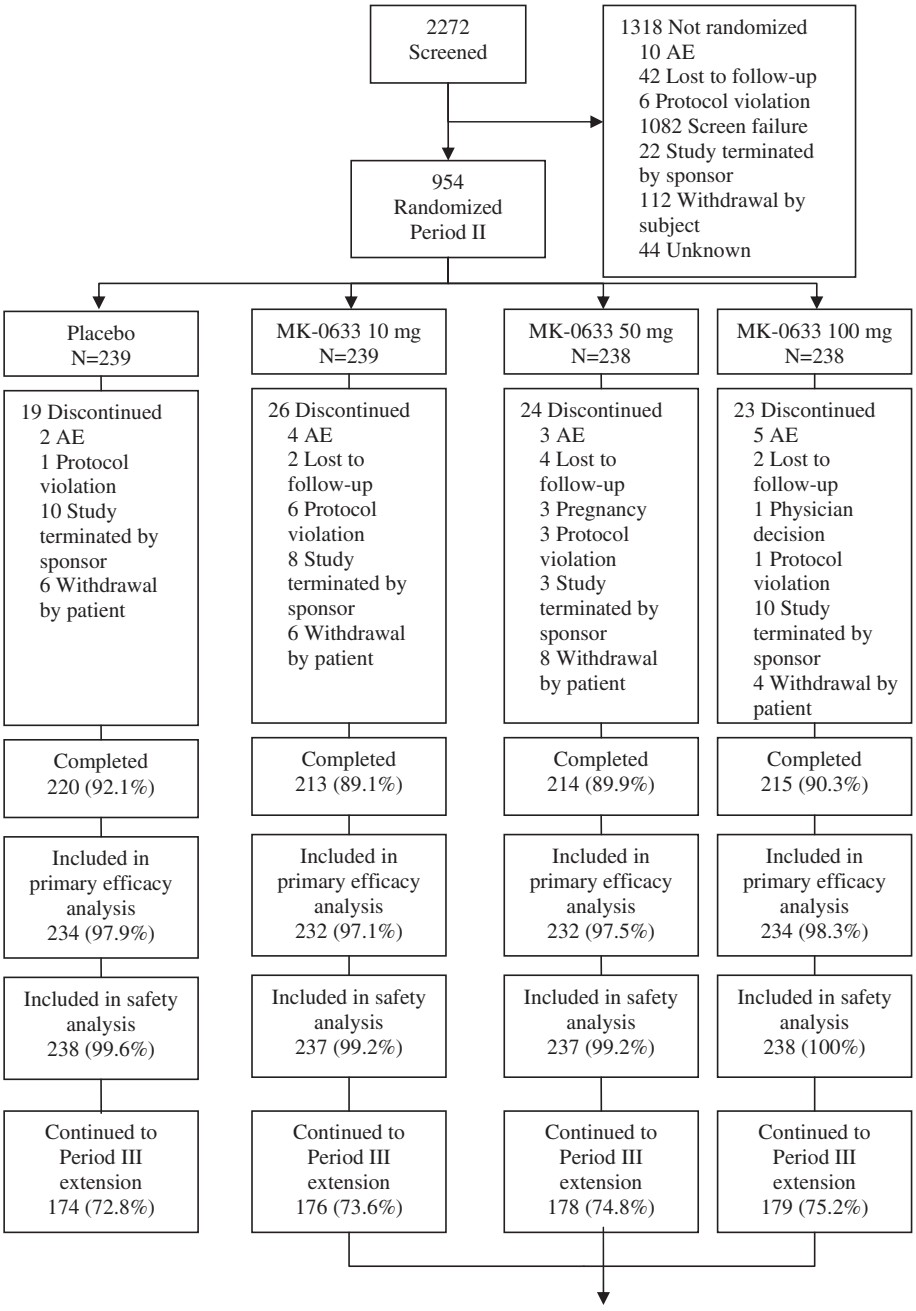

Figure 2 Patient flow through study.

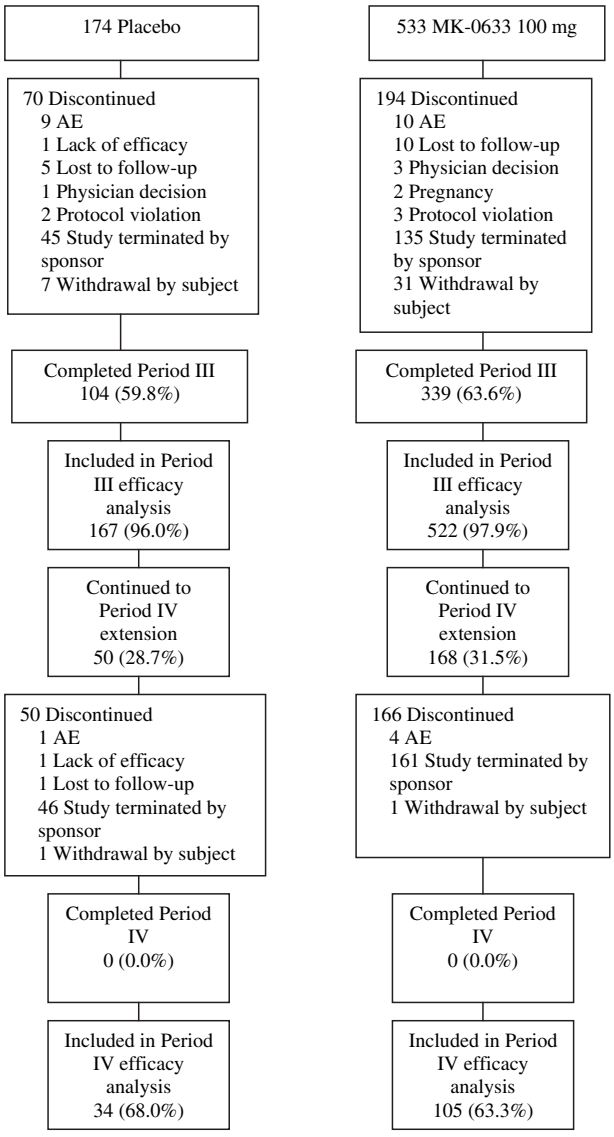

Figure 2 (continued)

Because there was only one primary endpoint, and because all other endpoints were considered supportive or exploratory, no further adjustment for multiplicity was performed.

With the planned 180 evaluable patients per group, the study had 92% power ($\alpha = 0.05$, two-sided *t*-test) to detect a 0.12 L treatment difference between an active group and placebo in the change from baseline in FEV_1, assuming a standard deviation of 0.34 L. In the subgroup of patients receiving ICS or ICS/LABA (planned to be 120 evaluable patients per group), the study had 80% power ($\alpha = 0.10$, two-sided *t*-test) to detect a 0.11 L difference in change from baseline in FEV_1.

Results

Patients

Patient flow through study is shown in Fig. 2. Approximately 90% of patients in each treatment group completed the base study (Period II). The most common reason for discontinuation from the study was early study termination by the sponsor. Baseline patient demographics were similar among treatment groups (Table 1).

Efficacy

Period II − 6 weeks

For the primary endpoint of the change from baseline in FEV_1 over the last 4 weeks of treatment, there was a statistically significant improvement from placebo through MK-0633 100 mg ($p = 0.004$ by the trend test), but not for MK-0633 50 mg (Table 2). The maximal effect was attained by Week 2 and remained generally stable through Week 6 (Fig. 3A). In general, the efficacy for the primary endpoint by concomitant medication stratum (i.e., ICS or ICS/LABA, none) was consistent for a given MK-0633 dose, as well as for other pre-specified subgroups (data not shown).

Table 1 Baseline patient characteristics - All randomized patients.

	Placebo $N = 239$	MK-0633 10 mg $N = 239$	MK-0633 50 mg $N = 238$	MK-0633 100 mg $N = 238$
Sex, *n* (%)				
Female	155 (64.9)	154 (64.4)	137 (57.6)	139 (58.4)
Age (years)				
Mean (SD)	44.0 (14.5)	43.2 (13.9)	43.6 (13.0)	42.8 (12.9)
Range	18.0 to 70.0	18.0 to 69.0	18.0 to 70.0	19.0 to 70.0
Body Mass Index (kg/m^2)				
Mean (SD)	26.5 (4.7)	26.7 (5.2)	26.0 (4.3)	26.1 (4.4)
Race, *n* (%)				
White	115 (48.1)	100 (41.8)	101 (42.4)	104 (43.7)
Black	9 (3.8)	13 (5.4)	14 (5.9)	6 (2.5)
Asian	62 (25.9)	69 (28.9)	71 (29.8)	73 (30.7)
Other	53 (22.2)	57 (23.8)	52 (21.8)	55 (23.1)
Smoking history, *n* (%)				
Ex-smoker	42 (17.6)	32 (13.4)	37 (15.5)	36 (15.1)
Concomitant asthma medications, n (%)				
None	84 (35.1)	84 (35.1)	87 (36.6)	88 (37.0)
ICS	76 (31.8)	86 (36.0)	74 (31.1)	77 (32.4)
ICS/LABA	79 (33.1)	69 (28.9)	77 (32.4)	73 (30.7)
FEV_1, mean (SD)				
L	2.03 (0.65)	2.02 (0.63)	2.07 (0.58)	2.04 (0.63)
% predicted	65.12 (10.89)	64.58 (10.73)	64.56 (10.52)	64.40 (11.62)

ICS: inhaled corticosteroid; LABA: long-acting β-agonist; SD: standard deviation.

There were no significant differences between MK-0633 and placebo for the secondary endpoints of daytime or nighttime symptom scores (Table 2). There was a modest but significant reduction from baseline in total daily β-agonist use through MK-0633 100 mg compared with placebo ($p = 0.022$). The differences from placebo for both AM and PM PEFR were significant through both MK-0633 100 mg ($p = 0.015$ and $p = 0.038$, respectively) and 50 mg ($p = 0.002$ and $p = 0.018$, respectively), as was the change in post-β-agonist FEV_1 ($p = 0.006$ and $p = 0.029$, respectively).

There were no significant differences between MK-0633 and placebo for measures of asthma control except for the percentage of patients who received at least one oral, intravenous, or intramuscular corticosteroid rescue in the MK-0633 100 mg and 50 mg groups compared with placebo ($p = 0.036$ for both) (Table 3).

Compared with placebo, there was a significant improvement in overall AQLQ through MK-0633 100 mg ($p = 0.030$) (Table 2) and significant improvements with all MK-0633 doses for the AQLQ symptom domain ($p = 0.025$ to 0.003) (data not shown). There were no significant differences in the other domains. There were significant differences through both MK-0633 100 mg ($p \leq 0.001$) and 50 mg ($p = 0.005$) compared with placebo for change in overall ACQ score (Table 2).

Period III — 24 weeks

MK-0633 100 mg was significantly more effective than placebo for the change from baseline in FEV_1 over Period III ($p = 0.034$) (Supplementary Table 1, Fig. 3b). The effect appeared to plateau around Week 8 and remain stable through Week 24. MK-0633 was significantly more effective than placebo for AM PEFR ($p = 0.006$), PM PEFR ($p = 0.004$), percentage of patients with at least one systemic corticosteroid rescue ($p = 0.020$), overall AQLQ score ($p = 0.029$), as well as the individual AQLQ domain scores of symptoms score ($p = 0.005$), emotions score ($p = 0.044$), and environment score ($p = 0.035$) (data not shown), the ACQ score ($p = 0.003$), eosinophils count ($p \leq 0.001$), and post-β-agonist FEV_1 ($p = 0.016$) (Supplementary Tables 1 and 2). There were no other significant differences between MK-0633 100 mg and placebo in Period III.

Period IV — 52 weeks

Fig. 3b, Supplementary Figure 1, and Supplementary Table 3 summarize the results from Period IV. Because of the limited data available for formal statistical analysis was not performed on efficacy endpoints.

Pharmacokinetics-pharmacodynamics

At the end of Period II, compared with placebo, MK-0633 substantially decreased the LTE_4/creatinine ratio in a dose-related fashion; median values for the 10 mg, 50 mg, and 100 mg doses were 28.3%, 4.6%, and 3.5% of the baseline values, respectively. By contrast, the LTE_4/creatinine level for placebo was essentially unchanged at 98.2% of the baseline value. Maximal (i.e., 90% pre-dose) inhibition of urinary LTE_4 occurred with MK-0633 plasma concentrations of approximately 1200 nM (Supplementary Fig. 2a). However, this plasma concentration of MK-0633 was associated with only small percentage change in FEV_1 (Supplementary Figure 2b).

Tolerability

Period II — 6 weeks

The frequency of clinical AEs was generally similar between treatment groups (Table 4). There were a total of 9 serious

Table 2 Main efficacy measures, Full analysis set, Period II.

Treatment	*N*	Baseline, mean (SD)	Change from baseline, LS mean (95% CI)	*p*-value vs. placebo[d]
FEV_1 (L)[a]				
Placebo	234	2.03 (0.65)	0.13 (0.09, 0.16)	–
MK-0633 10 mg	232	2.02 (0.64)	0.14 (0.10, 0.18)	0.586
MK-0633 50 mg	232	2.07 (0.58)	0.16 (0.12, 0.20)	0.201
MK-0633 100 mg	234	2.04 (0.63)	0.20 (0.16, 0.24)[e]	0.004
Daytime symptom score[a]				
Placebo	233	2.39 (0.90)	−0.25 (−0.34, −0.15)	–
MK-0633 10 mg	231	2.26 (0.80)	−0.30 (−0.40, −0.21)	0.404
MK-0633 50 mg	232	2.40 (0.85)	−0.26 (−0.36, −0.17)	0.828
MK-0633 100 mg	232	2.32 (0.78)	−0.32 (−0.42, −0.23)	0.369
Nighttime symptom score[a c]				
Placebo	188	0.71 (0.49)	−0.19 (−0.25, −0.14)	–
MK-0633 10 mg	177	0.74 (0.49)	−0.21 (−0.27, −0.16)	0.652
MK-0633 50 mg	168	0.64 (0.43)	−0.25 (−0.31, −0.19)	0.130
MK-0633 100 mg	161	0.77 (0.50)	−0.26 (−0.32, −0.20)	0.072
Total daily β-agonist use (puffs/day)[a]				
Placebo	233	3.55 (2.50)	−0.70 (−0.91, −0.48)	–
MK-0633 10 mg	231	3.83 (3.07)	−0.65 (−0.86, −0.43)	0.734
MK-0633 50 mg	232	3.65 (2.66)	−0.94 (−1.16, −0.73)	0.114
MK-0633 100 mg	232	3.55 (2.31)	−0.97 (−1.18, −0.75)[e]	0.022
AM PEFR (L/s)[a]				
Placebo	233	327.18 (104.03)	6.48 (2.28, 10.68)	–
MK-0633 10 mg	231	326.91 (93.84)	9.26 (5.05, 13.48)	0.325
MK-0633 50 mg	232	336.75 (96.35)	15.22 (11.01, 19.44)[e]	0.002
MK-0633 100 mg	232	333.34 (100.75)	12.23 (8.04, 16.43)	0.015
PM PEFR (L/s)[a]				
Placebo	233	315.08 (101.79)	9.18 (4.87, 13.49)	–
MK-0633 10 mg	231	315.82 (92.18)	11.99 (7.66, 16.32)	0.337
MK-0633 50 mg	232	326.64 (94.67)	16.13 (11.81, 20.45)	0.018
MK-0633 100 mg	231	320.66 (99.50)	14.55 (10.24, 18.86)	0.038
Asthma Quality of Life Questionnaire, overall score[b]				
Placebo	224	4.21 (1.13)	0.42 (0.31, 0.54)	–
MK-0633 10 mg	221	4.32 (1.07)	0.56 (0.44, 0.67)	0.101
MK-0633 50 mg	217	4.28 (1.02)	0.58 (0.47, 0.70)	0.056
MK-0633 100 mg	219	4.41 (1.12)	0.60 (0.49, 0.72)	0.030
Asthma Control Questionnaire, overall score[b]				
Placebo	226	2.41 (0.78)	−0.35 (−0.44, −0.25)	–
MK-0633 10 mg	221	2.34 (0.78)	−0.46 (−0.55, −0.36)	0.103
MK-0633 50 mg	216	2.39 (0.71)	−0.54 (−0.64, −0.44)	0.005
MK-0633 100 mg	219	2.38 (0.81)	−0.58 (−0.68, −0.49)	≤0.001
Post-β-agonist FEV_1 (L)[b]				
Placebo	210	2.50 (0.76)	−0.04 (−0.08, −0.00)	–
MK-0633 10 mg	207	2.47 (0.75)	−0.03 (−0.07, 0.01)	0.817
MK-0633 50 mg	208	2.50 (0.66)	0.02 (−0.02, 0.06)	0.029
MK-0633 100 mg	214	2.50 (0.72)	0.02 (−0.02, 0.06)[e]	0.006
Eosinophils (10^3/microL)[b]				
Placebo	213	0.35 (0.30)	−0.03 (−0.06, 0.00)	–
MK-0633 10 mg	210	0.40 (0.31)	−0.01 (−0.04, 0.03)	0.257
MK-0633 50 mg	214	0.41 (0.34)	−0.06 (−0.09, −0.03)[e]	0.268
MK-0633 100 mg	207	0.40 (0.32)	−0.05 (−0.08, −0.02)[e]	0.130

CI: confidence interval; FEV_1: forced expiratory volume in 1 s; LS: least squares; PEFR: peak expiratory flow rate; SD: standard deviation.
[a] Based on LDA model with factors for treatment; week (as categorical variable); concomitant corticosteroid stratum; baseline value as a covariate and a treatment-by-week interaction - Summary over the last 4 weeks of the treatment period.
[b] Based on ANCOVA model with factors for treatment, concomitant corticosteroid stratum and baseline value as a covariate - Measured at Week 6.
[c] FAS restricted to the subset of patients with nighttime symptoms at baseline.
[d] *p*-value for Tukey linear trend test through dose level.
[e] $p < 0.05$ vs. MK-0633 10 mg.

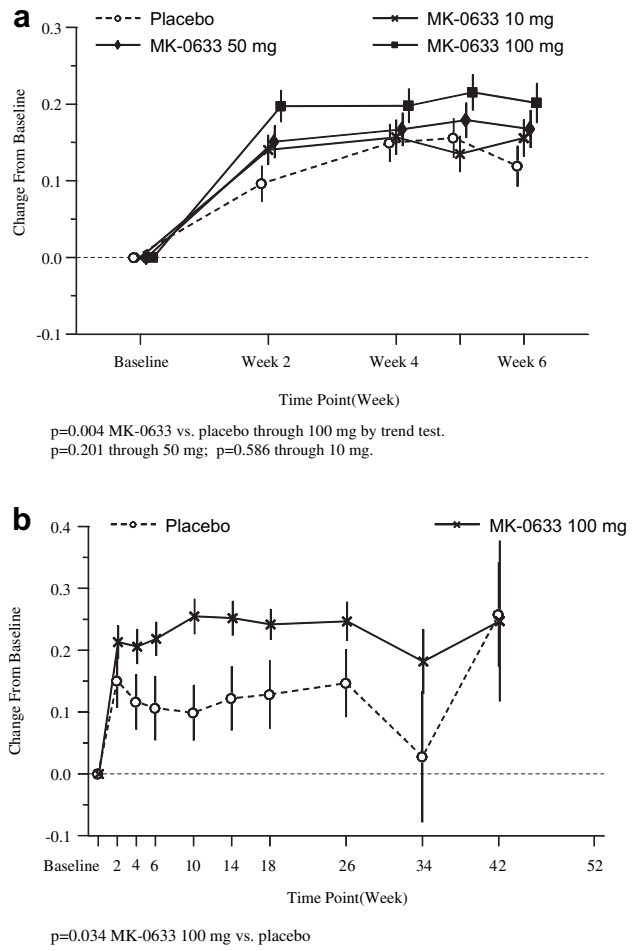

Figure 3 Primary efficacy measure: change from baseline in FEV_1 (L) over the last 4 weeks of treatment. A. Over 6 weeks (primary endpoint). B. Over optional extension periods. Full analysis set (only includes patients who entered the extensions for Fig. 2B).

AEs (4 AEs of asthma: 2 in placebo group, 1 in MK-0633 10 mg group and 1 in MK-0633 100 mg group; 1 AE of pyrexia and 1 AE of gastroenteritis in MK-0633 50 mg group; and AEs of Basal cell carcinoma, Sinusitis and Liver disorder in MK-0633 100 mg group), 2 of which resulted in discontinuations, one in the MK-0633 50 mg group (pyrexia) and one in the 100 mg group (asthma). There was 1 serious drug-related AE in a patient receiving MK-0633 100 mg, who had approximately 20-fold elevations in ALT and AST, which gradually returned to normal over several weeks after discontinuation of study drug. Thirteen (13) patients discontinued due to an AE, of which 4 were considered to be drug-related, 1 in the placebo group (drug eruption), 1 in the MK-0633 10 mg group (chronic cholecystitis), and 2 in the MK-0633 100 mg group (liver disorder and rash).

The rate of AEs of interest (discontinuations due to worsening of asthma and the percentage of patients meeting NAG discontinuation criteria) was low and similar between treatment groups (Table 4, Supplementary Tables 4 and 5).

There appeared to be a dose-related trend in AST and ALT elevations with MK-0633 compared with placebo (Table 5). After these results were unblinded for Period II, the study extensions were terminated early by the sponsor, based on an evaluation of the risks versus benefits of continued treatment. Patients in Periods III and IV at the time of study termination were discontinued from the study.

Period III and IV — 24 weeks and 52 weeks

The incidences of clinical AEs and LFT elevations in Periods III and IV were similar between MK-0633 100 mg and placebo (Tables 6—8).

Discussion

The purpose of this study was to explore the dose-response efficacy and tolerability of MK-0633, a 5-LO inhibitor, compared with placebo in adults with chronic asthma. We found that for the primary endpoint of the change from baseline in FEV_1 over the last 4 weeks of the main 6-week treatment period, MK-0633 was significantly more effective than placebo at the 100 mg dose, but not at the 50 mg dose. For the main study period, MK-0633 at various doses was also significantly more effective than placebo for several secondary endpoints. MK-0633 100 mg continued to be more effective than placebo over the first extension period for the primary endpoint in addition to most other efficacy measures, similar to that observed for the main treatment period. Because of the incidence of LFT abnormalities in the main study period, the optional study periods were terminated by the sponsor. Therefore, efficacy was not formally evaluated for the second extension period because of the small sample size due to study termination.

We found that MK-0633 achieved approximately 90% inhibition of urinary LTE_4 at a concentration of approximately 1200 nM, yet this was associated with a relatively modest change in FEV_1 from baseline. Indeed, based on the MK-0633 concentration-response curve, the dose-response plateau for FEV_1 was not likely achieved with 100 mg. Thus, the dose-response for LTE_4 and FEV_1 were distinct. Based on the PK/PD modeling of the data from this study, the dose to achieve a clinically meaningful increase in FEV_1 of 120 mL is approximately 4× that required to maximally inhibit LTE_4. The reason for the apparent incongruence between LTE_4 and FEV_1 in this study is unclear, and previous research regarding the relation between LTE_4 and asthma treatment response has been inconsistent. Reiss and colleagues found that, in patients with exercise-induced bronchoconstriction, urinary LTE_4 concentrations were significantly higher after exercise challenge in patients receiving placebo than in those receiving montelukast.[21] Similarly, in a study of intravenous montelukast in acute asthma in an emergency department setting, Green et al. found LTE_4 was significantly elevated during exacerbations compared with levels at follow-up 2 weeks later.[22] They also found a significant correlation between improvement in FEV_1 and decline in LTE_4 over the 2-week period. These results suggest that antileukotriene agents blunt LTE_4 production and that this effect is associated with improved lung function. Others have also found similar relationships between LTE_4 and lung function and the blunting effect of montelukast when measured over both relatively brief

Table 3 Other efficacy measures, Full analysis set, Period II.

Treatment	*N*	*n* (%)	Adjusted Odds Ratio (95% CI) vs. placebo	*p*-value vs. placebo[c]
Asthma attacks[a]				
Placebo	236	20 (8.5)	—	—
MK-0633 10 mg	235	25 (10.6)	1.2 (0.6, 2.2)	0.664
MK-0633 50 mg	235	12 (5.1)	0.5 (0.2, 1.1)[d]	0.067
MK-0633 100 mg	236	15 (6.4)	0.7 (0.3, 1.4)	0.112
Corticosteroid rescue[a]				
Placebo	236	19 (8.1)	—	—
MK-0633 10 mg	235	24 (10.2)	1.2 (0.6, 2.3)	0.650
MK-0633 50 mg	235	10 (4.3)	0.4 (0.2, 0.9)[d]	0.036
MK-0633 100 mg	236	12 (5.1)	0.5 (0.2, 1.2)	0.036
	N		LS mean (95% CI)	*p*-value vs. placebo[a]
Percentage of days with an asthma exacerbation[b]				
Placebo	236		16.01 (12.70, 19.32)	—
MK-0633 10 mg	235		18.00 (14.68, 21.32)	0.408
MK-0633 50 mg	235		13.96 (10.65, 17.27)	0.387
MK-0633 100 mg	232		12.77 (9.46, 16.09)[d]	0.066
Percentage of days with asthma control[b]				
Placebo	236		30.51 (25.94, 35.09)	—
MK-0633 10 mg	235		28.97 (24.38, 33.56)	0.624
MK-0633 50 mg	235		36.32 (31.74, 40.91)[d]	0.077
MK-0633 100 mg	236		31.32 (26.65, 35.77)	0.361

CI: confidence interval; SD: standard deviation.
[a] based on logistic regression model with terms for treatment, % predicted FEV_1 at baseline and concomitant corticosteroid stratum - Assessed at Week 6.
[b] based on LDA model with factors for treatment; week (as categorical variable); concomitant corticosteroid stratum; baseline value as a covariate and a treatment-by-week interaction. - Summary over the last 4 weeks of the treatment period.
[c] *p*-value for Tukey linear trend test through dose level.
[d] $p < 0.05$ vs. MK-0633 10 mg.

study periods (e.g., 8 days)[23] and longer observation periods (e.g., 4 weeks).[24] However, others have found little or no association between LTE_4 and response over longer period studies (4 weeks to year).[25,26]

Interestingly, early results with the 5-LO inhibitor zileuton showed a significant increase in FEV_1 (0.32 L) after 4 weeks of treatment despite urinary LTE_4 inhibition of only 39%,[27] supporting the possibility that changes in urinary LTE_4 and FEV_1 may not be highly correlated. It is notable, however, that in *ex vivo* whole blood assays, zileuton[28] produced greater than 90% LTB_4 inhibition, and MK-0633 at doses $\geq$100 mg (data on file) also produced greater than 90% LTB_4 inhibition.

There are several possibilities for these conflicting findings. First, as Rabinovitch et al. speculated, urinary LTE_4, which represents total body LTE_4 is a more general indicator of inflammatory response,[26] and does not accurately represent the concentration at sites of inflammation such as the small airways. In addition, meaningful associations between LTE_4 and lung function appeared to occur more commonly in acute asthma, more severe asthma, or shorter-term studies. Therefore, a significant correlation

Table 4 Number of patients with adverse experiences, All patients as treated, Period II.

	Placebo $N = 238$ n (%)	MK-0633 10 mg $N = 237$ n (%)	MK-0633 50 mg $N = 237$ n (%)	MK-0633 100 mg $N = 238$ n (%)
Clinical AE	88 (37.0)	93 (39.2)	83 (35.0)	95 (39.9)
Drug-related AE[a]	12 (5.0)	15 (6.3)	12 (5.1)	18 (7.6)
Serious AE	2 (0.8)	1 (0.4)	2 (0.8)	4 (1.7)
Discontinued due to AE	3 (1.3)	3 (1.3)	3 (1.3)	4 (1.7)
Discontinued due to worsening asthma[b]	2 (0.8)	0 (0.0)	1 (0.4)	2 (0.8)
Discontinued due to NAG[b]	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)

AE: adverse experience; NAG: N-acetyl-β-glucosaminidase.
[a] Determined by the investigator to be drug-related.
[b] $p>0.05$ for individual MK-0633 groups vs. placebo and for Cochran-Armitage trend test vs. placebo.

Table 5 Liver function test elevations, All patients as treated, Period II.

Criterion	Placebo		MK-0633 10 mg		MK-0633 50 mg		MK-0633 100 mg	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Alkaline Phosphatase (IU/L)								
Increase $\geq$ 100% and >ULN	0/236	(0.00)	0/234	(0.00)	1/232	(0.43)	2/234	(0.85)
Increase $\geq$ 50% and >1.5*ULN	0/236	(0.00)	1/234	(0.43)	0/232	(0.00)	2/234	(0.85)
Increase $\geq$ 50% and >2*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	1/234	(0.43)
>3*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)
>5*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)
Alanine Aminotransferase (IU/L)								
Increase $\geq$ 100% and >ULN	7/236	(2.97)	6/233	(2.58)	6/232	(2.59)	17/233	(7.30)
Increase $\geq$ 50% and >1.5*ULN	10/236	(4.24)	7/233	(3.00)	9/232	(3.88)	11/233	(4.72)
Increase $\geq$ 50% and >2*ULN	2/236	(0.85)	5/233	(2.15)	3/232	(1.29)	7/233	(3.00)
>3*ULN	2/236	(0.85)	2/233	(0.86)	0/232	(0.00)	5/233	(2.15)
>5*ULN	0/236	(0.00)	1/233	(0.43)	0/232	(0.00)	2/233	(0.86)
Aspartate Aminotransferase (IU/L)								
Increase $\geq$ 100% and >ULN	3/236	(1.27)	3/234	(1.28)	5/232	(2.16)	12/234	(5.13)
Increase $\geq$ 50% and >1.5*ULN	4/236	(1.69)	5/234	(2.14)	8/232	(3.45)	11/234	(4.70)
Increase $\geq$ 50% and >2*ULN	1/236	(0.42)	4/234	(1.71)	3/232	(1.29)	7/234	(2.99)
>3*ULN	0/236	(0.00)	2/234	(0.85)	0/232	(0.00)	6/234	(2.56)
>5*ULN	0/236	(0.00)	1/234	(0.43)	0/232	(0.00)	2/234	(0.85)
Bilirubin (mg/dL)								
Increase $\geq$ 100% and >ULN	3/236	(1.27)	3/234	(1.28)	3/232	(1.29)	1/234	(0.43)
Increase $\geq$ 50% and >1.5*ULN	2/236	(0.85)	0/234	(0.00)	2/232	(0.86)	0/234	(0.00)
Increase $\geq$ 50% and >2*ULN	0/236	(0.00)	0/234	(0.00)	1/232	(0.43)	0/234	(0.00)
>3*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)
>5*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)

ULN = Upper limit of normal range.

between LTE_4 and lung function might not be expected in our 6-week study in moderate chronic asthma.

Our observed mean absolute change in pre-bronchodilator FEV_1 with MK-0633 100 mg was 0.20 L, which is less than the changes of 0.23 L to 0.36 L observed in early and pivotal placebo-controlled trials of chronically administered zileuton.[13,27,29] The placebo-adjusted changes in FEV_1 were also smaller with MK-0633 (0.07 L) than for zileuton (approximately 0.11 L to 0.27 L). However, when accounting for baseline values, the changes observed with zileuton ranged from 12% to 16%, compared with a change of approximately 10% with MK-0633 100 mg in the present study.

Table 6 Number of patients with adverse experiences, All patients as treated, Period III.

	Placebo N = 174 n (%)	MK-0633 100mg N = 533 n (%)
Clinical AE	85 (48.9)	253 (47.5)
Drug-related AE[a]	11 (6.3)	28 (5.3)
Serious AE	1 (0.6)	3 (0.6)
Discontinued due to AE	5 (2.9)	8 (1.5)
Discontinued due to worsening asthma[b]	2 (1.1)	4 (0.8)
Discontinued due to NAG[b]	0 (0.0)	0 (0.0)

AE: adverse experience.
[a] Determined by the investigator to be drug-related.
[b] $p > 0.05$ for MK-0633 100 mg vs. placebo.

The corresponding changes from baseline with placebo were 6–7% in the zileuton studies, and 6% in our study. Thus, although the absolute changes in FEV_1 observed with zileuton were considerably higher than that observed in our study, the percentage changes from baseline were reasonably similar to that observed in our study. This observation, along with the similar effects of zileuton and MK-0633 on *ex vivo* LTB_4 inhibition and in FEV_1 suggest a generally similar efficacy profile between MK-0633 and zileuton.

There were no differences between treatment groups in the rates of overall clinical AEs or for the pre-specified AEs of interest (discontinuations due to worsening asthma or due to NAG). However, we observed a dose-dependent increase in the proportion of patients with ALT and AST elevations with MK-0633 compared with placebo during the main treatment period. Preclinical testing in mice at doses approximately 3× the maximal human AUC showed minimal treatment-related increases in ALT (<2× ULN), which was thought to be the result of adaptive response to enzyme induction. However, there were no transaminase changes in rats or dogs with doses of MK-0633 at exposures that were at least 7× the human exposure at the "no observed adverse effect level". As such, LFT abnormalities were not expected in humans, and thus, the exact basis of the apparent dose-related LFT elevations in Period II of the present study is unclear. Even more interestingly, the prevalence of LFT elevations during the extension periods was numerically greater in the placebo group than in the MK-0633 100 mg group, and a recent trial of MK-0633 100 mg in chronic obstructive pulmonary disease showed no difference in LFT elevations

Table 7 Number(%) of Patients with LFT Elevation, All patients as treated, Period III.

Criterion	Placebo		MK-0633 100 mg	
	n/N	(%)	n/N	(%)
Alkaline Phosphatase (IU/L)				
Increase ≥ 100% and >ULN	1/170	(0.59)	4/527	(0.76)
Increase ≥ 50% and >1.5*ULN	0/170	(0.00)	5/527	(0.95)
Increase ≥ 50% and >2*ULN	0/170	(0.00)	3/527	(0.57)
>3*ULN	0/170	(0.00)	1/527	(0.19)
>5*ULN	0/170	(0.00)	0/527	(0.00)
Alanine Aminotransferase (IU/L)				
Increase ≥ 100% and >ULN	15/170	(8.82)	37/525	(7.05)
Increase ≥ 50% and >1.5*ULN	12/170	(7.06)	29/525	(5.52)
Increase ≥ 50% and >2*ULN	8/170	(4.71)	15/525	(2.86)
>3*ULN	1/170	(0.59)	3/525	(0.57)
>5*ULN	0/170	(0.00)	1/525	(0.19)
Aspartate Aminotransferase (IU/L)				
Increase ≥ 100% and >ULN	11/170	(6.47)	23/527	(4.36)
Increase ≥ 50% and >1.5*ULN	12/170	(7.06)	24/527	(4.55)
Increase ≥ 50% and >2*ULN	8/170	(4.71)	14/527	(2.66)
>3*ULN	1/170	(0.59)	7/527	(1.33)
>5*ULN	1/170	(0.59)	2/527	(0.38)
Bilirubin (mg/dL)				
Increase ≥ 100% and >ULN	4/170	(2.35)	6/527	(1.14)
Increase ≥ 50% and >1.5*ULN	1/170	(0.59)	5/527	(0.95)
Increase ≥ 50% and >2*ULN	1/170	(0.59)	1/527	(0.19)
>3*ULN	1/170	(0.59)	0/527	(0.00)
>5*ULN	0/170	(0.00)	0/527	(0.00)

ULN = Upper limit of normal range.

versus placebo.[30] The pattern of LFT elevations in this study was that of asymptomatic, isolated ALT (and AST) elevations without associated alkaline phosphatase or bilirubin elevations, which is consistent with idiosyncratic hepatocellular injury, similar to that observed with zileuton.[13,14,29,31,32] This pattern and the lack of hepatic findings in preclinical or other clinical studies with MK-0633 suggest that there may be a class effect of 5-LO inhibitors on hepatic function, although additional investigations would be necessary for confirmation.

The efficacy observed with both zileuton and MK-0633 suggest that antileukotriene synthesis inhibitors may have a role in asthma treatment. Because zileuton and other antileukotriene synthesis inhibitors have never been directly compared with CysLT antagonists in a study of chronic asthma, the relative efficacy benefit of inhibiting leukotriene synthesis versus CysLT antagonism is unknown.

In conclusion, in patients with chronic asthma, MK-0633 was associated with a statistically significant but modest improvement in FEV_1 compared with placebo that was maintained for at least 24 weeks. There appeared to a dose-related increase in liver transaminases. The overall benefit-risk ratio did not support the clinical utility of MK-0633 in asthma.

Table 8 Number of patients with adverse experiences, All patients as treated, Period III and IV.

	Placebo $N = 50$ n (%)	MK-0633 100mg $N = 166$ n (%)
Clinical AE	27 (54.0)	100 (60.2)
Drug-related AE[a]	5 (10.0)	17 (10.2)
Serious AE	0 (0.0)	1 (0.6)
Discontinued due to AE	1 (2.0)	4 (2.4)
Discontinued due to worsening asthma	1 (2.0)	1 (0.6)

AE: adverse experience.
[a] Determined by the investigator to be drug-related.

Acknowledgments

The authors thank the Protocol 007 investigators, Sima Gaile, RN, BSN, for her contributions to the conduct of the study, Romana Petrovic, MS for her contributions to the statistical analysis, and Jennifer Pawlowski, MS for her help with the preparation of the manuscript.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.08.019.

Authorship

All authors are responsible for the work described in this paper, and were involved in at least one of the following:

[conception, design, acquisition, analysis, statistical analysis, interpretation of data] and [drafting the manuscript and/or revising the manuscript for important intellectual content]. All authors provided final approval of the version to be published. All authors meeting authorship requirements are listed, and no authors meeting requirements were excluded. The manuscript was collectively written by all named authors; no outside writing assistance was provided.

Financial support

This study was supported by Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc. The sponsor was involved in study design, collection, analysis, and interpretation of the data, writing of the manuscript, and decision to submit to submit the manuscript for publication.

Conflict of interest

Drs. Le Bailly de Tilleghem, Smugar, Hanley, and Knorr, are employees of Merck Sharp & Dohme Corp., who may potentially own stock and/or hold stock options in the Company. Drs. Wasfi and Reiss, and Ms. Petrovic are former employees of Merck. Dr. Villarán has served as a scientific advisor and has received research support from Merck, GlaxoSmithKline, AstraZeneca, Pfizer, Novartis, and Schering-Plough.

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